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13. ABSTRACT *(Maximum 200 Words)*

The purpose of this cross-sectional pilot study is to evaluate the effects on brain function and neurochemistry in elderly women (≧65 years old) of two common treatment regimens for breast cancer, tamoxifen and/or chemotherapy, and their interaction. The study has a 2x2 design with the two treatment regimens (tamoxifen and chemotherapy) as two independent variables. During the first year of the study, 49 women were recruited in 3 of the 5 groups (14 treated with tamoxifen (patient group), 18 women receiving estrogen replacement therapy (ERT) (positive control group), and 17 negative control subjects). On magnetic resonance spectroscopy (1H MRS), women who received tamoxifen (average 4.4 years) had no statistically significant differences in brain metabolite ratios compared to the negative control group. However, women who have received ERT (average > 20 years) showed increased N-Acetyl/creatine (NA/Cr) ratio (+8%; $p<0.01$) in the basal ganglia. These preliminary findings indicate that treatment with tamoxifen may not be associated with substantial negative effects on the brain. In contrast, since normal aging has been shown to be associated with decreases in NA/Cr, ERT may prevent or reduce some of the effects of normal aging on the brain. Ongoing efforts are being made to recruit subjects who received chemotherapy.

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"Brain Function, Structure, and Neurochemistry after Tamoxifen / Chemotherapy Assessed by Neuropsychologic Testing and 1H Magnetic Resonance Spectroscopy"

(4) INTRODUCTION

Loss of mental abilities represents a recognized threat to the quality of life of postmenopausal women with advancing age. Most recently, several reports have used a sensitive method (neuropsychological testing) to evaluate younger women with breast cancer after chemotherapy and hormonal modifying therapy (with tamoxifen), and found that a substantial percentage of these women had reduced mental abilities compared to women who were not treated with chemotherapy and hormonal modifying therapy. It also appears that these mental deficits are overlooked by the screening tests currently used in many large-scale breast cancer treatment and prevention studies, most likely because these simple screening tests become abnormal only when the brain is damaged to a moderate or severe degree. In the previous studies, most of the women with mental deficits obtained both chemotherapy and hormonal modifying therapy, so that it is unclear which of the two therapies caused the mental deficits. Furthermore, tens of millions of healthy women without breast cancer may soon obtain hormonal modifying therapy (with tamoxifen and possibly other drugs) to prevent future breast cancer; therefore, it is extremely important to know whether these drugs may cause injury to the brain and long-lasting problems with mental abilities. This study is designed to address these questions.

(5) BODY

Since the receipt of the funds in September 1999, we have made excellent progress towards accomplishing our goals. Altogether, we have evaluated 49 women between 65 and 80 years of age. During our initial year, we decided to focus on the three (of five) subject groups that did not involve chemotherapy, i.e. the tamoxifen, ERT and control subjects. Thus, of the 49 subjects evaluated to date, 14 are women with breast cancer who are treated with tamoxifen (patient group), 18 are control subjects who are receiving estrogen replacement therapy (ERT) (positive control group), and 17 are control subjects who have never received ERT (negative control group). The following paragraphs describe the research accomplished for each approved Task.

Task 1. Preparation for Subject Recruitment and Data Collection, Months 1-2

During the first 2 months of the project, we held several meetings among the key investigators and research associates to discuss and implement subject recruitment. Screening checklists were prepared, which allowed the research associates to evaluate many of the inclusion and exclusion criteria in brief telephone interviews. We decided to focus the first year of the study on the evaluation of the 3 subject groups that did not receive chemotherapy, i.e. breast cancer patients on tamoxifen only (tamoxifen group); healthy women receiving estrogen replacement therapy (ERT) (positive control group), and healthy women who did not receive ERT or tamoxifen (negative control group).

Task 2. Subject Recruitment and Data Collection, Months 3-32

During the initial project meetings, we decided to recruit women from several large ongoing

studies at Harbor-UCLA Medical Center. These studies, including the WHI and WHIMS studies, involve very large cohorts of women. After obtaining approval from the local IRB and the local and overall PIs on these studies, women in the eligible age range were contacted by mail, and were asked to call a study coordinator if they were interested in participating in this study. Women who contacted the study coordinator were then asked if they would be willing to perform a brief telephone screen, which was designed to assess most of the inclusion and exclusion criteria. After passing the brief telephone screen, eligible subjects were scheduled for a visit at the Harbor-UCLA Clinical Research Center. During this visit, we first obtained verbal and written informed consent, followed by a more detailed evaluation, including routine blood tests, detailed medical history, neurological examination, general functioning evaluation (Karnofsky scale), structured interviews for depressive symptoms [Geriatric Depression Scale - Short Form – 10 items, to exclude subjects with excessive depression (≥5 yes)] and anxiety/panic disorder (using Form A from Phase 2 of WHIMS: yes for anxiety questions and ≥4 out of 13 questions for panic disorders). Women who did not meet the study criteria were not allowed to participate any further.

Women who did meet the inclusion and exclusion criteria were then scheduled for an MRI / MRS scan and for neuropsychological testing (on two separate occasions). Altogether, our recruitment efforts have been extremely successful, since we were able to recruit nearly half of the total number of women (i.e. 49 out of 100 approved) in the first year of the study.

Task 3. Monitor Progress of Study. Months 3-32

As specified in the proposal, the Investigators, research assistants and research associates involved with the study met on an approximately monthly basis. During these meetings, we monitored the progress of the subject recruitment, and discussed and resolved problems with the study. However, there were no major problems with recruitment and the progress of the study, as evidenced by the large number of women recruited, i.e. we were able to recruit nearly half of the total number of subjects in the first (out of 3) year. Towards the end of this study year, some interim statistical analyses were performed and discussed during the meetings.

Task 4. Final Analysis and Publication. Months 33-36

Since the project is only at the end of year 1 (out of 3), we cannot perform a final data analysis.

Preliminary results

Although the study is just at the end of year 1, we are able to present some interim findings from the MRS measurements, based on the data of 49 subjects. The neuropsychological data provide a much greater number of variables, and are still being analyzed. Of the 49 subjects evaluated to date, 14 are women with breast cancer who are treated with tamoxifen (patient group), 18 are control subjects who are receiving estrogen replacement therapy (ERT) (positive control group), and 17 are control subjects who have never received ERT (negative control group). At this point in time, we are preparing an Abstract to be submitted to the Annual Meeting of the International Society of Magnetic Resonance in Medicine (ISMRM) and also a publication. To improve the statistical power for the preliminary analysis, we have pooled the data from the current study

with those from a prior pilot study, for a combined number of subjects of 75 (i.e. 26 data points were from the previous study). The clinical data for each of these groups are shown in Table 1.

Table 1

	Tamoxifen (n=14)	ERT (n=18)	Neg. controls (n=17)
Age	69.8 ± 4.9	71.4 ± 4.5	71.7 ± 4.5
Tamoxifen (years)	4.4 ± 1.7	N/A	N/A
ERT (years)	N/A	20.8 ± 10.5	N/A

We have analyzed the data and compared the three major cerebral metabolite ratios (NA/CR, CHO/CR, and MI/CR) on proton magnetic resonance spectroscopy between the negative control group and the tamoxifen and ERT groups, using separate t-tests. As Table 2 demonstrates, there are no statistically significant differences in the major metabolite ratios between women who take tamoxifen and those who do not (negative control group).

However, women who have received estrogen replacement therapy (ERT) for more than 2 years (on average for more than 20 years) have a statistically significant increase in the NA/CR ratio (+8%; $p < 0.01$) in the basal ganglia compared to healthy women who have not received estrogen. No other statistical differences in brain metabolism were observed between these two subject groups in the other 2 brain regions. These findings will be discussed below (Section 8).

Table 2

Region	Group	NA/Cr	Cho/Cr	MI/Cr
Hippocampus	Tamoxifen	1.33 ± 0.03	0.98 ± 0.02	0.90 ± 0.02
	ERT	1.33 ± 0.02	0.96 ± 0.03	0.88 ± 0.02
	Neg. Controls	1.34 ± 0.02	0.98 ± 0.02	0.90 ± 0.02
Frontal white matter	Tamoxifen	1.46 ± 0.03	1.06 ± 0.03	0.79 ± 0.02
	ERT	1.49 ± 0.04	1.04 ± 0.02	0.76 ± 0.02
	Neg. Controls	1.49 ± 0.03	1.08 ± 0.03	0.80 ± 0.02
Basal ganglia	Tamoxifen	1.31 ± 0.03	0.76 ± 0.02	0.61 ± 0.02
	ERT	1.37 ± 0.02*	0.75 ± 0.02	0.62 ± 0.02
	Neg. Controls	1.27 ± 0.03	0.75 ± 0.02	0.64 ± 0.02

Statistical significance: * $p < 0.01$ (ERT vs. negative controls)

(6) KEY RESEARCH ACCOMPLISHMENTS

- Created infrastructure to recruit study participants from ongoing large-scale studies at Harbor-UCLA Medical Center.
- Held monthly meetings to monitor the success of patient recruitment and resolve problems.
- Recruited 49 women in the correct age range and fulfilling all exclusion and inclusion criteria (14 in tamoxifen group; 18 ERT group; 17 negative control group).
- Performed interim statistical analyses.
- Preparing abstract and manuscript for submission.

(7) REPORTABLE OUTCOMES

As mentioned above, we are currently preparing an abstract and a manuscript describing our preliminary findings. Due to the early stage of the project, there are no other reportable outcomes.

(8) CONCLUSIONS

1. We did not find significant differences in the major metabolite ratios between the tamoxifen and negative control groups. Therefore, our preliminary data currently provide no evidence for abnormal brain chemistry in women who receive treatment with tamoxifen. Thus, our preliminary findings are in disagreement with our initial Hypothesis 2, that "women with a history of breast cancer (tamoxifen group) will show reduced concentration of NA (the neuronal marker) and increased concentration of MI (the glial marker)." However, please note that at this preliminary stage, we have only analyzed metabolite ratios, but not metabolite concentrations.

   Importantly, a lack of neurochemical abnormalities in women who have been treated with tamoxifen would be extremely good news for women with breast cancer or those who have a high risk for developing breast cancer. If confirmed in a larger longitudinal study with longer tamoxifen treatment periods, such a finding would suggest that it is probably safe to utilize for breast cancer prevention, at least with regards to potential side effects on the brain.

2. Our preliminary data also indicate that women who have been using estrogen replacement (ERT) for long periods of time (average >20 years) have a higher NA/Cr ratio in the basal ganglia compared to age-matched women who did not receive estrogen. Since normal aging has been shown to be associated with decreases in the NA/Cr ratio (1), the increased value in women on ERT may be interpreted (with caution) as "slowing of brain aging", at least in the basal ganglia region. This interpretation is in agreement with the result of other studies indicating positive effects of estrogen on the brain (2-6). Future analyses including the neuropsychological data will help us demonstrate whether the metabolite differences have any functional significance. Finally, the fact that we were able to detect the change in the NA/Cr ratio in these women exemplifies the sensitivity of ^{1}H MRS for assessing brain viability.

(9) REFERENCES

1. Chang L, Ernst T, Poland R, Jenden D. In vivo proton magnetic resonance spectroscopy of the normal human aging brain. Life Sci 1996;58:2049-2056.

2. Lindman K, Boone K, Lesser I, Miller B. Does estrogen replacement therapy protect cognitive ability in postmenopausal women? International Neuropsychological Society Meeting. Honolulu, 1998.

3. Resnick SM, Metter EJ, Zonderman AB. Estrogen replacement therapy and longitudinal decline in visual memory. A possible protective effect? Neurology 1997;49:1491-1497.

4. Baldereschi M, Di Carlo A, Lepore V, et al. Estrogen-replacement therapy and Alzheimer's disease in the Italian longitudinal study on aging. Neurology 1998;50:996-1002.

5. Kawas C, Resnick S, Morrison A, et al. A prospective study of estrogen replacement therapy and the risk of developing Alzheimer's disease: the Baltimore Longitudinal Study of Aging. Neurology 1997;48:1517-1521.

6. Yaffe K, Sayawa G, Lieberburg I, Grady D. Estrogen therapy in postmenopausal women: effects on cognitive function and dementia. JAMA 1998;279:688-695.

(10) APPENDICES

None.